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IPSO NITRATION REGIOSPECIFIC NITRATION VIA IPSO
NITRATION PRODUCTS (U) HARVEY MUDD COLL CLAREMONT CA
P C MYHRE 20 MAY 85 ARO-17572. 1-CH-H DRAG29-80-G-0009

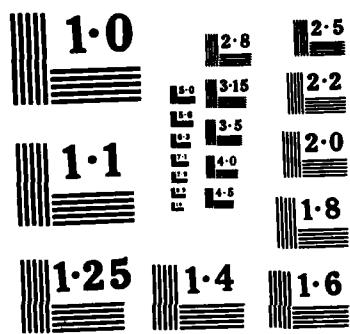
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) ABSTRACT. Work during the grant period has focused on developing efficient methods of preparing 4-alkyl-4-nitrocyclohexadienones and 4-alkyl-4-nitrocyclohexadienols by batch and flow processes. Detailed studies of the thermal and acid-catalyzed rearrangements of 4-alkyl-4-nitrocyclohexadienones have been made, leading to mechanistic assignments that may have broader implications to the mechanism of direct nitration of reactive aromatics with nitronium ion. Similarly, the hydrolysis reactions of nitrodiols in both acidic and neutral		

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aqueous media have been explored in detail. Studies of the reaction chemistry of nitrodiaryl halides and nitrodiaryl sulfonate esters have continued.

FINAL REPORT (EXTENDED ABSTRACT)

1. INTRODUCTION

This final report is organized as the initial proposal. The major objectives of this work are development of general methods of regiospecific synthesis of nitroaromatics. One promising approach involved the exploitation of the reactions of ipso nitration products, isolable but often labile initial products of nitration of alkylbenzenes and alkylphenol derivatives. The general pattern envisioned is shown in Scheme 1. In order to realize this objective, it is necessary to gain a better mechanistic understanding of these reactions. Thus, the effort has been divided between the synthesis of model compounds for synthetic exploration and the detailed mechanistic study of selected compounds.

2. 4-ALKYL-4-NITROCYCLOHEXADIENONES

The starting point of the projected syntheses outlined in Scheme 1 requires the preparation of 4-alkyl-4-nitrocyclohexadienones with appropriate substitution patterns. These nitrodi(enones) undergo thermal rearrangements under very mild conditions to yield 2-nitrophenols, and this rearrangement process has been found to be markedly catalyzed by strong acids. Our objectives were to: (1) prepare a representative set of nitrodi(enones), (2) optimize conditions for their preparation, (3) study the rates and characteristics of the thermal and acid-catalyzed rearrangement of these nitrodi(enones).

2.1 Preparation of 4-Alkyl-4-nitrocyclohexadienones

The majority of the nitrodi(enones) that have been prepared, Chart 1, were prepared in satisfactory yield by reaction of the phenyl acetate with acetyl nitrate solutions at -40 to -20 °C. Improved isolation procedures have been developed that allow bulk preparation and purification of some of these compounds in an afternoon. Others require more tedious and careful isolation. It was also found that nitrodi(enones) of the more highly alkylated phenols could be prepared in higher yield by direct low temperature nitration of the phenol itself. The reasons for these variations in optimal procedures are not clear. Low temperature crystallization allowed purification of most of the nitrodi(enones). Results with a recently acquired Chromatotron indicates that this rotating disk chromatographic procedure has the necessary speed and resolution to efficiently separate nitrodi(enones) from by-products. The technique is easily adapted to low temperature work, and is the preferred method for small scale preparation and isolation of these reactive substances.

Following a procedure brought to our attention by Professor A. Fischer and Dr. George Henderson, we have also explored solid state nitration of various alkylphenols. This procedure involves adsorbing concentrated nitric acid on alumina, followed by slurring the resulting solid with a methylene chloride solution of the alkyl phenol at -78 to -40 °C. The methylene chloride soluble products are then simply isolated by low-temperature filtration and evaporation of the solvent. This technique appears adaptable to a flow nitration system which would allow preparation of labile nitrodi(enones) in a low temperature flow system. This is conceived as the first step in a flow reactor that could allow

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selected preparation of a specified nitroarene isomer.

2.2 Rearrangements of Nitrodienones

Nitrodienones rearrange in a range of non-polar to polar, weakly acidic solvents to yield ortho-nitrophenols. In strong acid solution, unblocked nitrodienones react at rates that are several orders of magnitude faster to yield the same product. These two rearrangements are designated as a "thermal" and an "acid-catalyzed" rearrangement.

2.2.1 Thermal Rearrangements. The radical dissociation - recombination mechanism assigned to the thermal process has been generally accepted. The kinetics of thermal rearrangement of the set of nitrodienones prepared have been studied, and rates observed at a common temperature and solvent are also indicated in Chart 1.

Several of the nitrodienones listed are blocked from rearrangement by methyl groups at the two ortho positions, and their rates of decomposition to yield side-chain substitution products are much slower than rearrangement rates of comparably substituted unblocked nitrodienones. The rate of homolytic cleavage of the carbon nitro group bond could be estimated independently by measuring the rate at which the color of a stable radical, galvanoxyl, was bleached. This method was calibrated by measuring the rate of bleaching of galvanoxyl in the presence of unblocked nitrodienones such as 4-methyl-4-nitrocyclohexadienone. In the latter case, the bleaching rate was concordant with the directly measured rate of disappearance of product and the rate of formation of product. (This further confirms the mechanistic assignment for thermal rearrangement as involving a rate-limiting cleavage of the carbon - nitro group bond, and suggests that comparison of rates of galvanoxyl bleaching in blocked nitrodienones with rates of rearrangement in unblocked nitrodienones is fair.) It is to be noted that the rate at which 4-nitro-2,4,6-trimethylcyclohexadienone bleaches galvanoxyl is some 20 times faster than its rate of conversion to aromatic side chain substitution products.

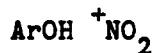
The rate data summarized in Chart 1 indicate relatively modest substituent effects. Substitution in the nitrodienones at C2 and C6 enhance the rate, while substitution at C3 and C5 retard the rate of rearrangement. The rate enhancement alkyl groups at C2 and C6 can be connected to the stabilization realized upon formation of the phenoxy radical intermediate. The retardation effect of alkyl groups at C3 and C5 can be associated with steric inhibition to the achievement of co-planarity of the 4-methyl group upon formation of the phenoxy radical. It should be noted, however, that the rates of thermal rearrangement of 4-nitro-4-ethyl- and 4-nitro-4-isopropylcyclohexadienone are actually slightly slower than those of the 4-methyl analog. The 4-*tert*-butyl analog reacts at about the same rate as 4-methyl-4-nitrocyclohexadienone.

An early investigation of the thermal rearrangement of nitrodienones included measurements of the extent of cross-over between reacting partners. These measurements have been extended and confirmed. In one study conducted in a hydrocarbon solvents ranging in viscosity from heptane to light mineral oil, it was demonstrated that the extent of cross-over was strongly dependent on solvent viscosity with the fraction of product formed by an intermolecular path going from 64% in heptane to 18% in mineral oil. NMR studies carried out with the use of nitrogen-15 labeled 4-methyl-4-nitrocyclohexadienone mixed with an equal amount of 4-methyl-4-nitrocyclohexadienone-1-Me-d₃, show that the extent of external return of nitrogen dioxide to the 4-methyl carbon of the 4-methylphenoxy radical was less than 15%.

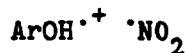
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Several unanswered issues connected to this work, as well as work by other investigators who have investigated some 2-alkyl-2-nitrocyclohexadienones, suggest to the writer that the phenyl nitrate ester is an intermediate of fleeting existence in these rearrangements. Experiments to test this hypothesis remain to be carried out.

2.2.2 Acid-Catalyzed Rearrangements. Direct measurements of the rate of rearrangement of representative nitrodienones in 10-75 wt% sulfuric acid show the onset of acid catalysis at about 45% sulfuric acid, with rate enhancements at the higher end of the acidity range of at least several hundred-fold. We assume that the catalysis is associated with proton transfer from the acid to the carbonyl oxygen, and that the subsequent rearrangement reaction involves a starting material that has a molecular composition identical with that of the parent phenol and nitronium ion. Thus, this rearrangement is useful to study the details of nitration of a phenols with nitronium ion. It has been suggested that the intermediate in these rearrangements is the encounter pair 1, but it is also possible that this pair could be formulated as the radical cation-radical pair 2. In some respects the distinction is subtle, and the evidence obtained previously is not compelling.



1



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On the basis of the kinetic analysis for bimolecular nitration of reactive aromatics, it can be predicted that tests for intra- *versus* intermolecularity in this acid-catalyzed rearrangement should show substantial intramolecular character. Indeed, this proves to be the case. Doubly labeled 4-methyl-4-nitrocyclohexadienone-*Me-d*₃, ¹⁵N was allowed to react with an equal amount of unlabeled 4-methyl-4-nitrocyclohexadienone in a range of solvents. By contrast with the thermal reaction in hydrocarbon solvents which show extensive cross-over, there is less than 5% cross-over in strong acid solutions. Some of this small percentage of observed crossover may be owing to adventitious thermal rearrangement.

One means of discriminating between 1 and 2 involves demonstration of electron transfer. In principle, electron transfers can occur at rates comparable to molecular diffusion. An attractive probe of the structure of the pair is a test for electron transfer, and one such reaction is shown in equation 1.



The problem then is: How can an electron transfer be realized and clearly reported? Electron transfers of the type shown in eq 1 can occur at or near the diffusion limit, but recombination of the pair, 1 or 2, normally occurs at a rate that is at least marginally faster than the separation of the pair. Our initial approach was to use a blocked nitrodienone, 4-nitro-2,4,6-trimethylcyclohexadienone as the substrate. In sulfuric acid this nitrodienone decomposes to yield 2,6-dimethylquinone, 2,6-dimethyl-4-nitrophenol, 3-nitro-2,4,6-trimethylphenol, and a range of side-chain substitution products. When 4-nitro-2,4,6-trimethylcyclohexadienone labeled with carbon-13 at the 4-methyl carbon and nitrogen-15 at the nitro group was allowed to react in the presence of an equimolar amount of the unlabeled nitrodienone, the 3-nitro-2,4,6-trimethylphenol product (a product of a formal 1,2-shift of the nitro group) was shown by mass spectrometry to form by an intramolecular path.

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When the same acid-catalyzed reaction was conducted in the presence of an equimolar amount of mesitol (in this case, the nitrodienone used was unlabeled, but the mesitol was labeled), a portion of the 3-nitro-2,4,6-trimethylphenol was found to form by an intramolecular path.

It was also noted that when the reaction of 4-nitro-2,4,6-trimethylcyclohexadienone was conducted in the presence of a ten-fold excess of mesitylene, the yield of side-chain substitution products (benzyl alcohol, benzyl esters, benzaldehyde, 2,4,6-trimethylphenylnitromethane) were greatly reduced and two diphenylmethane derivatives (4-hydroxy-2',3,4',5,6'-pentamethyldiphenylmethane, and 2,2',4,4',6,6'-hexamethyldiphenylmethane) were formed in compensation. It was shown that the first of these diphenylmethane derivatives was formed initially, and this was more slowly converted to the second diphenylmethane product. It seems clear that these diphenylmethanes result from Friedel-Crafts alkylation of mesitylene, first by the 3,5-dimethyl-4-hydroxybenzyl cation to yield the first diphenylmethane derivative. Acid-catalyzed transalkylation then accounts for the subsequent conversion to the second derivative. A likely path of formation of the 3,5-dimethyl-4-hydroxybenzyl cation appeared to be by the net loss of a hydrogen atom from the corresponding aromatic radical cation.

Thus, a critical experiment was devised: Reaction of 4-nitro-2,4,6-trimethylcyclohexadienone and an equimolar mixture of labeled mesitol in 76-91% sulfuric acid in the presence of mesitylene afforded the normal range of products — 2,6-dimethylquinone, 4-nitro-2,6-dimethylphenol 3-nitro-2,4,6-trimethylphenol, side-chain substitution products, and diphenylmethane derivatives. The diphenylmethanes and other side-chain substitution products consisted of a nearly equimolar mixture of the unlabeled and labeled material. Some of the 3-nitro-2,4,6-trimethylphenol product also contained a label. The label could have only come from the unlabeled mesitol.

The data suggest that under the reaction conditions an aromatic radical cation - radical pair is formed by decomposition nitrodienone conjugate acid, and this aromatic radical cation can be induced to accept an electron from a donor, mesitol. The result of this electron exchange is reported by the labeled side-chain substitution products such as the diphenylmethane derivatives and the evidence of cross-over in the nitration product formed.

When the acid-catalyzed reactions of unblocked nitrodienones (4-methyl-4-nitro- and 3,4-dimethyl-4-nitrocyclohexadienone) were conducted in the presence of equimolar amounts of mesitol and excess mesitylene, a similar pattern of results was obtained. In each case diphenylmethanes were formed in significant yield (10-15% compared with 30-40% in the case of 4-nitro-2,4,6-trimethylcyclohexadienone), and traces (1-3%) of both 3-nitro-2,4,6-trimethylphenol and 2,6-dimethyl-4-nitrophenol were also detected by GC/MS.

More recent studies of the acid-catalyzed rearrangement of carbon-13 labeled 4-methyl-4-nitrocyclohexadienone in the presence of excess unlabeled *p*-cresol again show evidence of as much as 25% cross-over in the 2-nitro-4-methylphenol product.

The combined results strongly suggest that conjugate acids of nitrodienones fragment homolytically to yield a radical cation - radical pair, and that the aromatic radical cation can be intercepted in part by an electron transfer agent. The occurrence of this electron transfer is reported by the products formed.

Our current plans are to expand these studies further and refine some of the measurements. More importantly, we plan to explore the utility of CIDNP effects in the nitrogen-15 spectra in the reaction of selected nitrodienones in acid media. The combination of the product evidence and spectral evidence should provide a much firmer base for the understanding of these reactions.

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3. 4-ALKYL-4-NITROCYCLOHEXADIENOLS

The preferred batch mode of preparation of 4-alkyl-4-nitrocyclohexadienone involves low temperature reduction with sodium borohydride in methanol followed by vacuum evaporation and low temperature liquid-liquid extraction. As a complementary method, means of preparing 1,4-dialkyl-4-nitrocyclohexadienols by addition of alkylolithium reagents to nitrodienones have also been worked out. We have worked on refining these methods and improving the ease with which they can be conducted. We have also explored methods for solid state reduction of nitrodienones as an improvement and as a possible means of conducting sequential nitration, reduction, and acidolysis in a flow system. Additional studies of solvolytic reactions of nitrodienols in neutral aqueous solvents and in acid solutions have been carried out.

3.1 Reductions of Nitrodienones in Solution.

Continued refinement of this procedure has allowed the purification of (Z)-4-methyl-4-nitrocyclohexadienol as a colorless, crystalline solid. This crystalline 1,4-adduct of nitric acid and toluene is extremely labile at room temperature and even decomposes slowly (months) on storage at -40 °C. However, it can be handled without significant decomposition when held in dilute solution of an organic solvent.

3.2 Solid State Reduction of Nitrodienones.

The labile character or secondary nitrodienols of methylbenzenes is such that they will never become items on the commercial chemical market. A better way of preparing these materials for use in the reaction chemistry under consideration would be of great value. Solid state reductions offer distinct advantages, and reductions of nitrodienones by sodium borohydride supported on alumina and silica have been studied. As anticipated the reduction of nitrodienones is several orders of magnitude slower on these solid state reducing agents than model compounds such as cyclohexanone. Currently, optimal conditions for reduction appear to require two hours at -10 °C with maximum yields of the nitrodienol of approximately 50%. Continued exploration of reaction conditions will be required in order to incorporate this reduction procedure as part of a flow system that could carry a phenol through a sequence of reactions to an isomerically pure arene.

3.3 Reactions of Nitrodienols

Under acid catalyzed reaction conditions, nitrodienols or nitrodiennyl acetates lose water or acetic acid to yield the ispo ion. Given an open position on the ring, the nitro group typically migrates by one or a series of 1,2-shifts to yield the corresponding nitroarene with the nitro group fixed at the nearest open position. This is the general path envisioned to yield "ortho" nitration products. In neutral or mildly acidic aqueous media, the nitro group leaves preferentially as nitrite anion, and the corresponding 1-hydroxy- or 1-acetoxycyclohexadienyl cation rearomatizes by loss of a proton. If the hydroxyl group is converted into a better leaving group (a halide or a sulfonate ester) nucleophilic displacements may be mounted at C1 before loss of the nitrite ion. The net result of this sequence, a displacement followed by elimination, is the synthesis of a "para" substitution product, and this is the path envisioned for

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regiospecific "para" nitration. Exploration of the scope of these reactions has continued during the grant period and results are summarized below.

3.3.1 Acidolysis of Nitrodienols and Nitrodiene Acetates. Work in this and other laboratories indicates that acid-catalyzed reformation of the ipso ion and subsequent nitro group migration to the nearest open position is essentially quantitative for nitrodienols and nitrodiene acetates that have two or more alkyl groups. However, the acidolysis of 4-methyl-4-nitrocyclohexadienol affords a maximum yield of about 60% of ortho-nitrotoluene. The remainder is p-cresol or p-cresyl acetate. This result is attributable to the absence of a donor group attached to the pentadienyl carbon framework of the ipso ion formed in this system and the presence of such a donor group in the pentadienyl carbon framework of the ion formed by loss of the nitro group as nitrite ion. We have tried a range of acid conditions to increase the yield of 2-nitrotoluene in this acidolysis without success.

3.3.2 Hydrolysis of Nitrodienols. Nitrodienols and nitrodiene acetates solvolyze in aqueous alcohol to yield the corresponding phenol or phenyl acetate. The reaction is formally an elimination of the elements of nitrous acid and has been characterized as an E1-like elimination. Representative nitrodienols solvolyze at rates that are 20-30 times greater than those of the corresponding nitrodiene acetates. Further, deuterium substitution at C1 showed that nitrodienols undergo solvolysis in aqueous ethanol with attendant migration of deuterium to C2 or C6. Typically about 30% of the original deuterium label is found at C2 or C6 when a representative nitrodienol is solvolyzed. By contrast no more than 1% deuterium is retained upon solvolysis of the nitrodiene acetate. We interpret these results to indicate that the 1-hydroxycyclohexadienyl cation that forms by the departure of a nitrite ion leaving group can be partitioned along two paths. The first is direct transfer of the C1 hydrogen to the solvent. The second involves an intramolecular 1,2-shift of the hydrogen to form a cyclohexa-2,4-dieneone conjugate acid which can then undergo a dienone-phenol rearrangement to yield rearomatized product. This latter reaction has been repeatedly observed in microsome mediated oxidations of aromatic hydrocarbons and during solvolytic studies of appropriately labeled arene oxides and has been called the "NIH shift." The occurrence of an NIH shift in these reactions does allow one to project more detailed studies of this type of intramolecular rearrangement. One facet that has not been studied is the effect of different substituents on the intermolecular/intramolecular partitioning of the hydrogen transfer, and some aspects of these studies are discussed in section 3.3.3.

The initial kinetic and hydrogen retention studies of nitrodienol solvolysis were carried out with mixtures of stereoisomers. In the case of 4-nitro-4-methylcyclohexadienol, crystalline samples of both the unlabeled and deuterium labeled materials have been subjected to kinetic study, and the deuterium retention has been reinvestigated with the labeled compound. The results quantitatively corroborate the earlier findings.

3.3.3 Reactions of 4-Alkyl-4-nitrocyclohexadienyl Halides and Methanesulfonates. In order to realize regiospecific "para" nitration, it is necessary to displace the oxygen function in nitrodienols or nitrodiene acetates with a better leaving group. Then, as indicated above, a nucleophilic displacement of this leaving group before elimination of the elements of nitrous acid affords the "para" substitution product. We have been able to realize these reactions with the use of 4-nitro-3,4,5-trimethylcyclohexadienyl systems. This is owing

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to the fact that this nitrodiaryl acetate can be readily converted to the corresponding crystalline nitrodiaryl chloride, and this substance can then be used to prepare 4-nitro-3,4,5-trimethylbenzene, as well as a range of related products of displacement and elimination, in good yield. Similar results have been obtained more recently with the use of 3,4-dimethyl-4-nitrocyclohexadienyl chloride, although this nitrodiaryl chloride is less readily prepared from the nitrodiaryl acetate. We have been unable to prepare 4-methyl-4-nitrocyclohexadienyl chloride or bromide from the corresponding nitrodiaryl acetate for reasons that are related to the discussion given in section 3.3.1. To circumvent this problem, we have developed a procedure to prepare the 4-methyl-4-nitrocyclohexadienyl methanesulfonate from 4-methyl-4-nitro-cyclohexadienol. This methanesulfonate ester is quite reactive and must be stored at -80 °C, but it can be used for displacement-elimination chemistry to yield *p*-nitrotoluene in good yield. Studies with a range of other nucleophiles also indicate that this procedure is applicable to regiospecific placement of a many other nucleophiles at the para position in toluene. It is clear, however, that the current synthetic methodology involves too many manipulative steps with very fragile, reactive compounds. The results establish the principles, but continued simplifications of procedure will be necessary in order to make the application of these principles truly useful.

4. Related Miscellaneous Studies

During the grant period a group of related studies were undertaken that do not fit neatly into the general outline of the report. These are summarized here.

4.1 Acetyl Nitrate Adducts of Furan

The earliest reported adducts of acetyl nitrate to aromatic systems came from studies of the nitration of furan. In collaboration with Professor Arnulf Vollmar, California State Polytechnic University, Pomona, we have developed efficient means of preparation and purification of the diastereomeric adducts formed by nitration of furfural diacetate and methyl furoate with acetyl nitrate. The solvolytic chemistry of these adducts has been studied in detail. We have also surveyed the nitration reactions of furan, 2-methylfuran and 2,5-dimethylfuran. Adducts have been obtained in all cases, but we have not been successful as yet in the isolation and purification of crystalline adducts of the simpler furan derivatives, although we anticipate that this will be possible with the use of refined chromatographic procedures.

4.2 Nitration of *o*-Xylene with Nitryl Chloride

Literature reports indicate the nitration of *o*-xylene with nitryl chloride gives an unusually high yield of 4-nitro-*o*-xylene, although speculation concerning the reasons for this seem lacking. It occurred to us that nitryl chloride could react with *o*-xylene to form the adduct, 3,4-dimethyl-4-nitrocyclohexadienyl chloride, which could suffer direct elimination of the elements of hydrogen chloride to form 4-chloro-*o*-xylene, or also react with available nitrite in the system to yield 3,4-dimethyl-1,4-dinitrocyclohexadiene and then suffer elimination to yield 4-nitro-*o*-xylene. Mr. Gary May carried out a number of preliminary experiments to test this hypothesis. Typical reaction conditions involved low temperature addition of nitryl chloride of nitryl chloride to a

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mixture of α -xylene and a Lewis acid (typically titanium tetrachloride). Aromatic chlorination product was a major component of the reaction in all runs conducted, but under optimal conditions nitration product comprised some 35% of the reaction mixture. Both the 4-nitro- and the 4-chloro- α -xylene proved to be dominant over the 3-isomer by better than 3:1. The results suggest that reaction of nitryl chloride with methyl benzenes such as α -xylene may indeed involve an addition-elimination sequence and that this elimination sequence may be perturbed by the intrusion of a displacement process before the elimination yields the rearomatized product. Continued study of these systems seem warranted.

4.3 Direct Detection of Ipso Ions by Very Low Temperature C-13 NMR

During the past five years, the writer has been involved with CPMAS NMR studies of carbocations. This has resulted in the measurement of spectral parameters of a number of carbocations and the detection of the limiting static spectra of a number of carbocations that undergo very rapid degenerate rearrangement. Attempts have been made to apply these techniques to the study of ipso ions in the solid state. To date no definitive spectra have been obtained, although the methodology for the collection of such spectra is now well established. Work will continue in the area during the coming year.

Scientific Personnel Supported by this Project

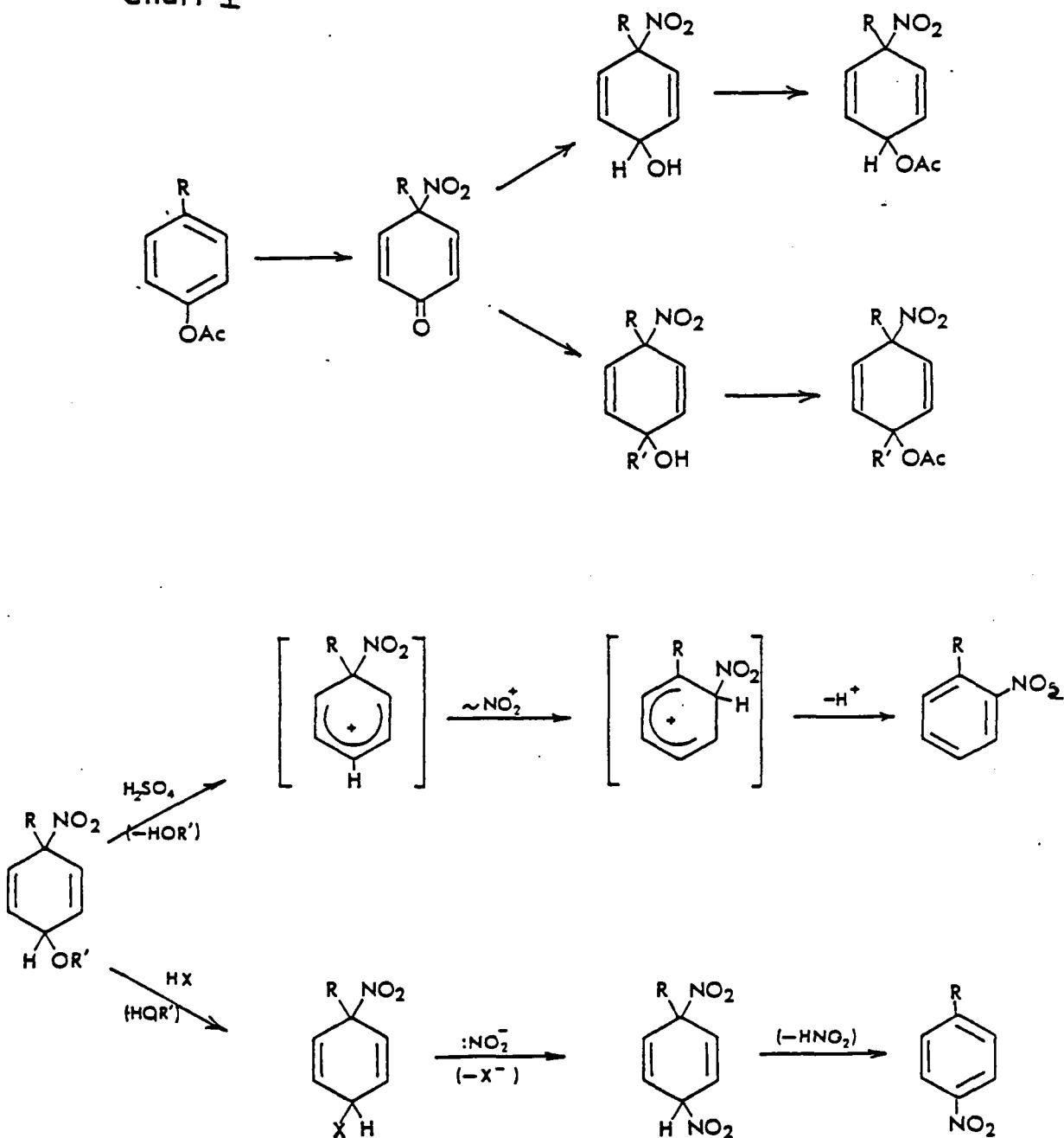
Name	Degree	Current Position
Ann McDermott	B.S. ('81)	Ph.D. candidate, UC Berkeley
Jeanne Haubrich	B.S. ('81)	Ph.D. candidate, UC Berkeley
Melissa Dale		Chemist, Metropolitan Water District
Timothy Heil	B.S. ('81)	Ph.D. candidate, U Wisconsin, Madison
Gary L. May	B.S. ('82)	Chemist, Chevron Research
Nancy Phillips	B.S. ('82)	Ph.D. candidate, U Wisconsin, Madison
William Krause	B.S. ('83)	M.S. Biomedical Engineering, UCLA medical student, Dartmouth
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Earl Rutenbur	B.S. ('84)	Ph.D. candidate, U Texas, Austin
Louis Kuo	B.S. ('84)	Ph.D. candidate, Northwestern U
Fred Elsner	B.S. ('85)	Ph.D. candidate, UC San Diego



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Chart I

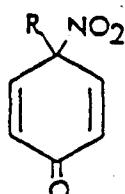


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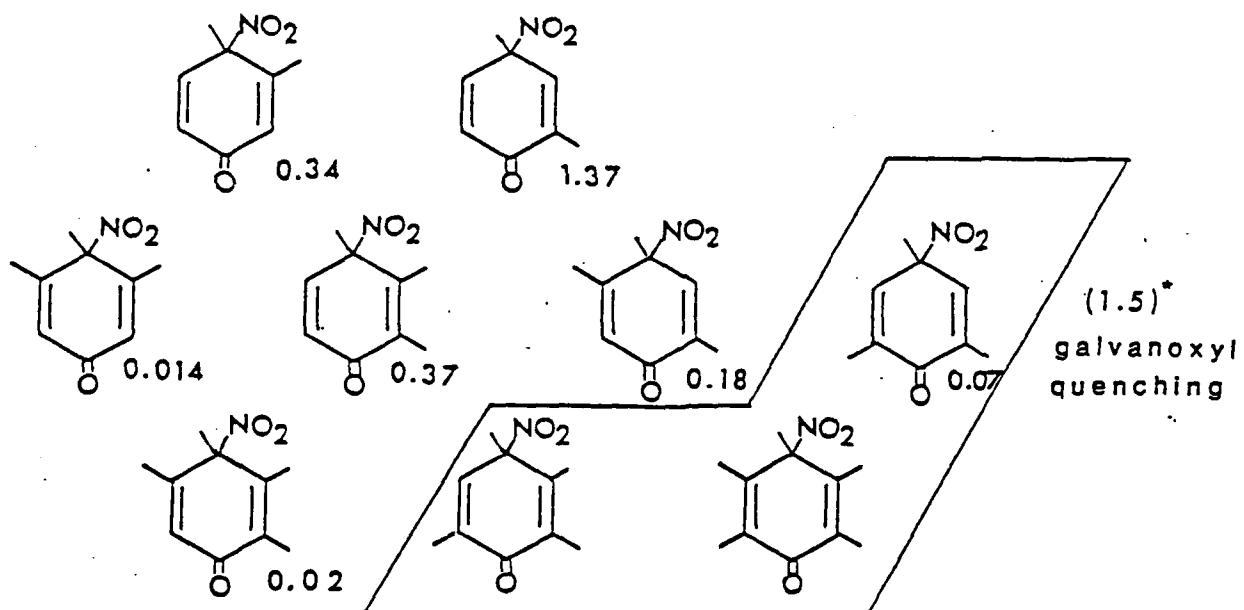
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Figure 1

Rates of Thermal Decomposition ...heptane at 25 C



R = Me 1.0 ($4.7 \times 10^{-4} \text{ sec}^{-1}$)
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 iPr 0.40



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